

REMARKS

A. Regarding the Amendments

Claim 1 has been amended as set forth in the above "Listing of the Claims." As amended, the claims are supported by the specification and the original claims. In particular, the amendments to claim 1 are supported, for example, at page 4, lines 6-7 and page 11, lines 12-21. Claim 16 has been added. Support for new claim 16 may be found, for example, in Example 1 and Figure 1 of the application, as filed. Thus, upon entry of the amendments, claims 1-13, 15 and 16 will be pending.

B. Entry of the Information Disclosure Statement

The Examiner's entry of the duplicate Information Disclosure Statement requested by the Patent and Trademark Office and mailed February 14, 2003 is acknowledged. The Examiner's notation that the Information Disclosure Statement mailed January 21, 2003 is a duplicate is also acknowledged and is acceptable to Applicant.

C. Rejection Under 35 U.S.C. § 112

Applicant respectfully traverses the rejection of claims 1-13 and 15 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to point out and distinctly claim the subject matter of the invention. In particular, the claims are rejected for use of the term "wherein the antisense nucleic acid is capable of having activity and is flanked by the stem loop structures..."

Applicant respectfully draws the Examiner's attention to the amended language of claim 1. As amended, the language specifies that the antisense included in the construct has activity such that it suppresses gene expression. By the amendment, the language "capable of" has been removed. Support for this amendment may be found in the specification at, for example, page 4, lines 21-22 and page 8, line 18 to page 9, line 19. The Examiner, in the Office Action mailed May 6, 2003, stated that "[t]he specification as filed refers to suppression of gene expression

using the antisense constructs..." As the language of the claim now names a specific activity and is no longer directed to "capable of having activity," it is respectfully submitted that the amended claim particularly points out and distinctly claims the subject matter of the invention. Therefore, claims 1-13 and 15 meet the definiteness requirement of 35 U.S.C. §112, second paragraph. Accordingly, withdrawal of the rejection is requested.

Applicant respectfully traverses the rejection of claims 1-13 and 15 under 35 U.S.C. § 112, first paragraph, for containing subject matter allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the invention at the time of filing of the Application. In particular, it is alleged in the Office Action mailed May 6, 2003 that claims 1-13 and 15 are not limited to an antisense construct flanked with 5' and 3' U1 snRNA structures and that Applicant was not in possession of a representative number of species of the claimed constructs at the time the invention was made. Applicant respectfully traverses.

It is noted that the rejection is based on the guidelines of MPEP 2163. In Paper No. 24, it was noted by the Examiner that the language of MPEP 2163 states that:

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." (Emphasis added.)

The alleged basis of the present rejection is that Applicant was not in possession of a representative number of species of the claimed constructs at the time the invention was made. However, it is noted that none of the guidelines of MPEP 2163 is absolute, or exclusive of the other guidelines. The repeated use of the conjunction "or" emphasizes that the requirements may be met independently, but the end of the cited paragraph states that the guidelines may be taken

in combination. Applicant respectfully submits that the written description requirement has been met through a combination of identifying characteristics of the claimed constructs.

Applicant has presented a representative number of species of constructs containing antisense flanked with 5' and 3' stem loops. Specifically, support for inclusion of stem loop structures and examples thereof are present in the specification at, for example, page 7, line 24 to page 8, line 6, Figure 1 and pages 23-29. While it is noted that U1 snRNA structures are utilized, these structures are meant to be exemplary and not limiting. In addition to the written description of species of the constructs, the specification contains an actual reduction to practice utilizing U1 snRNA structures in the Examples. Figure 1 contains a reduction to drawing of the exemplary construct. The specification sets forth numerous relevant, identifying characteristics, such as that the stem loop has a folding pattern that forms hairpins, the stem loops of the construct will flank the antisense and they can be derived from yeast or from mammals such as human, porcine or bovine, for example, and that the structure is preferably unmodified. Additionally, the stem loops serve the functional purpose of stabilizing the construct (specification page 7, line 4). When taken together, it is respectfully submitted that these characteristics meet the written description requirement for the stem loops of the construct of the invention. One of skill in the art would have known, from the combination of these elements, that Applicant was in possession of the genus of the claimed nucleic acid constructs.

Support for various antisense structures within the construct is also found throughout the specification which, taken in combination, adequately supports Applicant's assertion that the written description requirement has been met. Actual reduction to practice has been shown by the inclusion of an antisense in the construct of the Examples (e.g., see page 23, lines 7-23). Reduction to drawings is shown by the specification of an antisense in the construct of Figure 1. Additionally, in the specification, numerous relevant, identifying characteristics are set forth, for example, at page 8, line 18 to page 9, line 19 and in the Examples, such as possessing a structure that is directed to a target nucleic acid. One of skill in the art can identify a target sequence and

its associated antisense. Additionally, functional characteristics coupled to the above structural characteristics are also disclosed in the specification, for example, the fact that the structure of the antisense binds to the target and interferes with translation of the RNA, such that the construct as a whole suppresses gene expression of the target.

By the showing of a combination of reduction to practice, reduction to drawings and identifying characteristics and related function, the specification shows a construct containing the stem loops and antisense, as claimed. Accordingly, it is Applicant's position that claims 1-13 and 15 meet the written description requirement of 35 U.S.C. §112, first paragraph. Withdrawal of the rejection is therefore respectfully requested.

Applicant respectfully traverses the rejection of claims 1-13 and 15 under 35 U.S.C. § 112, first paragraph, for allegedly being non-enabled for nucleic acid constructs where the antisense is capable of having activities other than suppression of gene expression.

The Examiner's attention is again drawn to the amendment of claim 1 in the Listing of the Claims above. As amended, claim 1 requires that the antisense suppress gene expression, rather than stating that the antisense is capable of having activity. As stated by the Examiner on page 6 of the Office Action mailed May 6, 2003, the specification is "enabling for nucleic acid constructs for suppressing gene expression." As such, one of skill in the art would have been able to practice the present invention, as the amended claims specify a construct that suppresses gene expression. Therefore, claims 1-13 and 15 meet the enablement requirement of 35 U.S.C. §112, first paragraph. Accordingly, the removal of the rejection is requested.

D. Rejection Under 35 U.S.C. § 102

Applicant respectfully traverses the rejection of claims 1-13 under 35 U.S.C. 102(a) as allegedly anticipated by Michienzi. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed.

Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir., 1990). Applicant respectfully submits that Michienzi does not teach all elements of claims 1-13.

Initially, it is noted that the claims 1-13 recite a nucleic acid construct with a 5' step loop structure, an antisense nucleic acid and a 3' stem loop structure. The stated purpose of the claimed construct of the invention is to provide a general method of delivery for antisense sequences (see, for example, abstract, page 1, lines 7-9, page 4, lines 2-3). In particular, the constructs suppress gene expression of the target gene. In contrast, the invention of Michienzi describes delivery of ribozymes and it is noted on page 7219, column 2, second paragraph that "[t]he use of disabled ribozymes has allowed us to show that degradation is mainly due to catalytic cleavage rather than antisense effect." In fact, in the Results section at page 7220, column 2, paragraph 3, Michienzi specifically states that derivatives with a C to G substitution were utilized "[t]o control for the antisense effect of ribozymes." Therefore Michienzi teaches away from the constructs of the claimed invention, which deliver an antisense nucleic acid molecule to cells to specifically provide an antisense effect. In the claimed invention, when ribozymes are optionally used (see, for example, claim 8), it is in a construct containing both an antisense nucleic acid and a ribozyme as a supplementary activity.

Additionally, it is noted that the stem loops of the claimed invention are not modified. The term "unmodified" is defined in the specification as "the folding pattern of the stem loop structure is not compromised by alterations in the nucleic acid sequence of the naturally occurring molecule." The Examiner, in Paper No. 24 points out language in the specification that the claimed stem loops, even where unmodified, may contain modifications, as long as those modifications do not change the stabilization function and hairpin formation of the stem loop. (Specification, page 7). Applicant does not dispute this statement, however, it is noted that these changes or insertions cannot be insertion of the antisense sequence. Claim 1 recites a construct with a 5' loop, an antisense and the 3' loop in 5'-3' order. The claimed invention does not allow for the presence of the antisense within the stem loop. Michienzi, on the other hand, teaches a

construct where the ribozyme sequence has been inserted in place of a 22 nucleotide region of the natural sequence of the stem loop. Rationale for the placement of the ribozyme at this location is set forth on page 7220, column 2, paragraph 1. Therefore, it is respectfully submitted that the Michienzi reference does not teach a nucleic acid construct with the 5' to 3' orientation of the claimed construct, nor a construct containing an antisense, where the antisense suppresses gene expression, nor a construct where the stem loop structures flank the antisense and the antisense is not within the 3' or 5' stem loop structures.

Michienzi teaches nucleic acid constructs in which the stem loop III of U1 snRNA is modified by the addition of a hammerhead ribozyme. Even where Michienzi used antisense to control for the antisense effect, it was done by modification of a stem loop and addition of a hammerhead ribozyme with a conserved C substituted by a G, such that the ribozyme lost its cleavage ability. Accordingly, all constructs taught by Michienzi contain modified stem loop structures.

Applicant respectfully disagrees with the Examiner's assertion that the "unmodified" construct of Michienzi contains unmodified stem loops. The unmodified U1-Rz construct referred to by the Examiner on page 7219, column b, lines 39-42, is shown graphically in Figure 1. Michienzi's "unmodified" U1-Rz construct is a U1 snRNA that has a hammerhead ribozyme nucleic acid sequence inserted into the stem-loop III nucleic acid sequence. Michienzi's "modified" construct (U1-Rz_m) is a construct in which the nucleic acid sequence forming the catalytic core of the hammerhead, *i.e.*, CUGAUGA, has C replaced by G (see page 7220, column b, lines 26-32). Such modification renders the catalytic activity of the ribozyme inactive. Thus, the "unmodified" constructs of Michienzi have stem loop structures that are modified by the presence of ribozyme nucleic acid. They contrast with the "modified" constructs (U1-Rz_m) in which the ribozyme nucleic acid insert is itself modified. Michienzi does not teach any nucleic acid constructs having unmodified stem loop structures. Accordingly, Michienzi can not anticipate Applicant's invention.

Finally, the Examiner's attention is drawn to three specific requirements in the language of claim 1. First, it is required that the antisense nucleic acid be flanked by the stem loop structures. Second, it is required that the antisense nucleic acid suppress gene expression. Third, it is required that the antisense nucleic acid not be within either the 5' or the 3' stem loop structure. Michienzi does not describe administration of a ribozyme utilizing a construct with these characteristics.

As Michienzi does not teach all of the elements of the claimed invention, it is respectfully submitted that Michienzi does not anticipate the claimed invention under 35 U.S.C § 102(a). Withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

In summary, for the reasons set forth herein, Applicant maintains that claims 1-13, 15 and 16 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

In re Application of:

Harry C. Dietz

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Page 11

PATENT

Attorney Docket No.: JHU1400-1

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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